EFFICACY OF PAMIDRONATE IN REDUCING SKELETAL EVENTS IN PATIENTS WITH ADVANCED MULTIPLE MYELOMA

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Abstract *Background.* Skeletal complications are a major clinical manifestation of multiple myeloma. These complications are caused by soluble factors that stimulate osteoclasts to resorb bone. Bisphosphonates such as pamidronate inhibit osteoclastic activity and reduce bone resorption.

Methods. Patients with stage III multiple myeloma and at least one lytic lesion received either placebo or pamidronate (90 mg) as a four-hour intravenous infusion given every four weeks for nine cycles in addition to antimyeloma therapy. The patients were stratified according to whether they were receiving first-line (stratum 1) or second-line (stratum 2) antimyeloma chemotherapy at entry into the study. Skeletal events (pathologic fracture, irradiation of or surgery on bone, and spinal cord compression), hypercalcemia (symptoms or a serum calcium concentration ≥12 mg per deciliter [3.0 mmol per liter]), bone pain, analgesic-drug use, performance status, and quality of life were assessed monthly.

Results. Among 392 treated patients, the efficacy of treatment could be evaluated in 196 who received pamidronate and 181 who received placebo. The proportion of patients who had any skeletal events was significantly lower in the pamidronate group (24 percent) than in the placebo group (41 percent, P<0.001), and the reduction was evident in both stratum 1 (P=0.04) and stratum 2 (P=0.004). The patients who received pamidronate had significant decreases in bone pain and no deterioration in performance status and quality of life. Pamidronate was well tolerated.

Conclusions. Monthly infusions of pamidronate provide significant protection against skeletal complications and improve the quality of life of patients with stage III multiple myeloma. (N Engl J Med 1996;334:488-93.)

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M ULTIPLE myeloma is a cancer of plasma cells that is characterized by osteolytic bone destruction.[1] The bone disease can lead to pain, pathologic fractures, spinal cord compression, and hypercalcemia and is a major cause of morbidity and mortality in affected patients.[2] These complications result from increased osteoclastic resorption of bone that is not accompanied by increased bone formation.[3] The increase in osteoclastic activity in patients with multiple myeloma is mediated by the release of osteoclast-stimulating factors by myeloma cells.[4,5]

Bisphosphonates inhibit osteoclastic activity and are effective in the treatment of cancer-associated hypercalcemia.[6,7] These drugs have been evaluated as adjunctive therapy in the treatment of myeloma bone disease.[8-10] When added to chemotherapy in patients with newly diagnosed myeloma, oral etidronate was ineffec-tive,[8] whereas oral clodronate inhibited the progression of osteolytic bone lesions but did not reduce bone pain or rates of pathologic fracture.[10] Pamidronate disodium, a second-generation bisphosphonate, is a potent inhibitor of bone resorption at doses that do not affect bone mineralization.[11] Ninety milligrams of pamidronate was found to be the most effective dose for normalizing serum calcium concentrations in a dose-ranging trial in patients with cancer-associated hypercalcemia.[12] The results of open-label trials suggest that pamidronate may be effective in reducing the skeletal complications of multiple myeloma.[13,14] Therefore, we conducted a randomized, double-blind study comparing monthly pamidronate with placebo for the reduction of skeletal events in patients with multiple myeloma.

METHODS

Patients

We enrolled ambulatory adult patients with Durie–Salmon[15] stage III multiple myeloma and at least one osteolytic lesion at 88 study sites (constituting the Myeloma Aredia Study Group) in the United States, Canada, Australia, and New Zealand from August 1990 through June 1993. Each patient had received a regimen of chemotherapy that had not changed during at least the two months before enrollment and had an estimated life expectancy of at least nine months.

Patients were ineligible if they had had a skeletal event during the two weeks before enrollment, a serum creatinine concentration greater than 5.0 mg per deciliter (442 μmol per liter), ascites or a serum total bilirubin concentration greater than 2.5 mg per deciliter (43 μmol per liter), or an abnormal echocardiogram. Patients were also excluded if they had been treated with a bisphosphonate (except as part of this study) during the 60 days before enrollment or were so treated at any time during the trial, or if they had been treated with a corticosteroid (except as part of the chemotherapeutic regimen), calcitonin, or plica-

mycin during the 2 weeks before enrollment. During the trial, changes in the chemotherapeutic regimen were permitted.

Study Design

Before randomization, the eligible patients were classified into two strata according to their type of antimyeloma therapy at entry into the study. Stratum 1 included patients receiving first-line chemotherapy (initial treatment or treatment for disease that was controlled with a single regimen), and stratum 2 included patients receiving second-line or subsequent chemotherapy (regimens used after initial chemotherapy to control myeloma had failed). In each stratum, the patients were randomly assigned on a 1:1 basis to receive either 90 mg of pamidronate disodium (Aredia, Ciba–Geigy, Summit, N.J.) administered in 500 ml of 5 percent dextrose in water or placebo (500 ml of 5 percent dextrose in water). Each study treatment was administered as a four-hour intravenous infusion every four weeks for nine cycles. A computer-generated list of the patients' study assignments was provided to the pharmacist at each study site; the other study personnel remained unaware of the assigned treatments.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics review board at each institution. All the patients provided written informed consent. The results obtained during the nine planned cycles are reported here, except for survival data, which were collected from the time of randomization through March 1, 1994.

Assessments

At each of the nine monthly visits, the patients were evaluated by a physician who was unaware of the treatment-group assignments. Any decisions regarding chemotherapy or radiotherapy were made by physicians who were unaware of the study-drug assignments. The occurrence of any skeletal events (defined as pathologic fracture, irradiation of or surgery on bone, and spinal cord compression) was recorded. Additional assessments included a physical examination, the evaluation of bone pain, and the determination of scores for analgesic-drug use as previously described,[16] scores for Eastern Cooperative Oncology Group (ECOG) performance status,[17] and scores for quality of life on the Spitzer index.[18] The occurrence of any hypercalcemia (as defined by the presence of symptoms or a serum calcium concentration, corrected for the serum albumin concentration, of at least 12.0 mg per deciliter [3.0 mmol per liter]) was also noted. Several patients required more than 9 months (that is, up to 12) for the assessment of skeletal events to be completed, because of delays in the infusion of the study drug. A complete survey of bones, including long bones, was conducted during the month before treatment and after six and nine cycles. The response of bone lesions was evaluated by a radiologist who did not know the patients' treatment assignments. This response was assessed on the basis of criteria adapted from those of the International Union against Cancer for responses in breast cancer.[19] These criteria use recalcification as a marker for the healing of osteolytic lesions, but pathologic fractures are not considered to constitute evidence of progressive disease in bone.

Studies performed in the clinical laboratory at each visit included a complete blood count; a platelet count; serum-chemistry tests; measurement of serum osteocalcin, bone alkaline phosphatase, immunoglobulins, and beta$_2$-microglobulin; urinalysis; and a urine test for Bence Jones proteins. Two-hour fasting urine samples for measurement of calcium, hydroxyproline, and creatinine were collected before each infusion of study drug.

Statistical Analysis

Kaplan–Meier estimates of the time from randomization to the first occurrence of a skeletal event were calculated; the log-rank test was used for comparisons between study treatments. The proportions of patients who had skeletal events by the end of three cycles (up to 126 days), six cycles (up to 210 days), and nine cycles (the duration of the entire study) were estimated from the Kaplan–Meier curves for the time to the first event. In addition, the proportion of patients in each group who had skeletal events was estimated by calculating the number of patients who had such an event divided by the number of

patients in each treatment group. The chi-square test was used to compare these proportions.

Changes from base line in bone pain, scores for analgesic-drug use, ECOG performance-status scores, scores on the quality-of-life index, serum concentrations of myeloma protein and beta$_2$-microglobulin, and bone metabolic markers were analyzed by the Wilcoxon signal-rank test and the Wilcoxon rank-sum test for comparisons within and between treatment groups, respectively. Kaplan–Meier estimates of the time from randomization until death (with the data censored as of March 1, 1994) were calculated for each treatment group and compared by the log-rank test. All statistical tests were two-sided.

RESULTS

A total of 392 patients were enrolled in the study; 203 patients received pamidronate, and 189 received place-

Table 1. Characteristics of the 377 Patients with Skeletal Manifestations of Multiple Myeloma Who Could Be Evaluated, According to Treatment Group.*

CHARACTERISTIC	PAMIDRONATE (N = 196)	PLACEBO (N = 181)
Sex — no. of patients (%)		
Male	108 (55)	109 (60)
Female	88 (45)	72 (40)
Age (yr)	64±10	63±10
Stratum — no. of patients (%)†		
1	133 (68)	114 (63)
2	63 (32)	67 (37)
Myeloma subtype — no. of patients (%)		
IgA	28 (14)	43 (24)
IgG	111 (57)	85 (47)
Light chain	42 (21)	46 (25)
Other‡	15 (8)	7 (4)
Time since diagnosis — no. of patients (%)		
<1 yr	78 (40)	85 (47)
≥1 yr	118 (60)	96 (53)
Time since start of initial chemotherapy — mo		
Stratum 1		
Median	8	6
Mean	17±22	14±19
Stratum 2		
Median	44	32
Mean	45±24	43±38
Serum beta$_2$-microglobulin — mg/liter	2.9±2.2	3.2±2.1
Serum creatinine — mg/dl§	1.1±0.3	1.2±0.6
Hemoglobin — g/dl	11.6±1.9	11.2±1.7
Pain score — no. of patients (%)¶		
0	37 (19)	28 (16)
1–3	73 (37)	73 (41)
4–9	86 (44)	79 (44)
ECOG performance score — no. of patients (%)‖		
0	46 (23)	44 (24)
1 or 2	133 (68)	126 (70)
3 or 4	17 (9)	11 (6)

*Plus–minus values are means ±SD.

†Patients were stratified at entry according to whether they were receiving a first-line (stratum 1) or a second-line (stratum 2) chemotherapeutic regimen.

‡"Other" includes myelomas of the IgE subtype, nonsecretory tumors, and myelomas of unknown subtype.

§To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

¶Pain scores were calculated by multiplying the score for pain severity (graded from 0 to 3) by the score for pain frequency (graded from 0 to 3). A pain score of 0 indicates no pain, and a pain score of 9 indicates constant, severe pain. In the placebo group, a base-line pain score was not obtained for one patient.

‖ECOG denotes Eastern Cooperative Oncology Group. A score of 0 denotes fully active; 1, restricted with regard to strenuous activity; 2, ambulatory; 3, restricted to limited self-care; and 4, completely disabled.

bo. All the treated patients were included in the assessments of safety and the analyses of survival. The 15 patients enrolled at one study site were excluded from the analysis of efficacy because of deviations from the protocol with respect to the blinding procedures used in the study. Thus, the evaluation of efficacy was based on 377 patients (196 receiving pamidronate and 181 receiving placebo) studied at 87 sites. The number of patients studied per site ranged from 2 to 41, and six sites enrolled 10 or more patients.

At entry into the study, the characteristics of the 377 patients who were included in the analysis of efficacy in the two treatment groups were similar (Table 1). Also, there were no significant differences between the groups in the number of lytic bone lesions, scores for analgesic-drug use, or quality-of-life scores (data not shown). Seventy-eight percent of the patients completed nine cycles of study treatment. The median period of follow-up was 9 months for the assessments of efficacy (as measured by a reduction in skeletal events) and safety and 17 months for the determination of survival. The chemotherapeutic regimens in the two groups were similar before and during the study. Specifically, there was no difference between the pamidronate group and the placebo group in the use of oral melphalan and prednisone or more aggressive regimens (treatment with multiple alkylating drugs or doxorubicin).

Skeletal Events

The time to the first skeletal event (Fig. 1) was significantly less in the placebo group than in the pamidronate group ($P = 0.001$ by the log-rank test). The times to the first pathologic fracture ($P = 0.006$) and the first radia-

Table 2. Occurrence of Skeletal Events by the End of the Third, Sixth, and Ninth Cycle of Treatment.

TYPE OF EVENT	PATIENTS WITH EVENT (%)			ESTIMATED PROPORTION WITH EVENT*		
	PAMIDRONATE (N = 196)	PLACEBO (N = 181)	P VALUE†	PAMIDRONATE (N = 196)	PLACEBO (N = 181)	P VALUE
Any‡						
3 cycles	20 (10)	38 (21)	0.004	11	22	
6 cycles	41 (21)	58 (32)	0.01	24	34	
9 cycles	47 (24)	74 (41)	<0.001	28	59	0.001
Pathologic fracture						
3 cycles	12 (6)	16 (9)	0.32	6	9	
6 cycles	27 (14)	34 (19)	0.19	16	22	
9 cycles§	34 (17)	54 (30)	0.004	22	52	0.006
Radiation treatment to bone						
3 cycles	14 (7)	29 (16)	0.007	7	17	
6 cycles	24 (12)	36 (20)	0.04	13	21	
9 cycles	28 (14)	40 (22)	0.05	16	33	0.05
Hypercalcemia						
3 cycles	1 (1)	9 (5)	0.007	1	5	
6 cycles	4 (2)	10 (6)	0.07	2	6	
9 cycles	7 (4)	11 (6)	0.25	7	6	0.25

*Proportions are estimated from Kaplan–Meier curves. P values are for the comparison between groups by the log-rank test.

†For the comparison between groups by the unadjusted chi-square test.

‡Except hypercalcemia.

§There were 50 vertebral and 20 nonvertebral fractures in the pamidronate group, as compared with 91 and 44, respectively, in the placebo group.

tion treatment to bone ($P = 0.05$) were also significantly less in the placebo group. The proportions of patients who had any skeletal event and who were given radiation treatment to bone during follow-up were significantly lower in the pamidronate group than in the placebo group after three, six, and nine cycles of therapy, whereas the proportion of patients in the pamidronate group who had new pathologic fractures was significantly lower than in the placebo group only after nine cycles of therapy (Table 2). The proportion of patients with hypercalcemia was significantly lower in the pamidronate group than in the placebo group after only three cycles of therapy. The proportions of patients in both groups who had spinal cord compression associated with vertebral compression fracture or who required surgery on bone were small (2 and 4 percent, respectively).

Stratum

In both strata, the proportion of patients who had any type of skeletal event was significantly lower in the pamidronate group than in the placebo group (Table 3). The proportion who had pathologic fractures was significantly lower in the pamidronate group than in the placebo group in stratum 1, and the proportion who had radiation treatment to bone was significantly lower in the pamidronate group than in the placebo group in stratum 2.

Radiologic Assessment

Eighty-two percent of the patients in both groups were assessed radiologically at base line and at six months, nine months, or both. Of those who could be evaluated radiologically, 84 percent of patients in the pamidronate group and 79 percent of patients in the pla-

P = 0.001

NO. AT RISK
Pamidronate 196   170   146   97   20
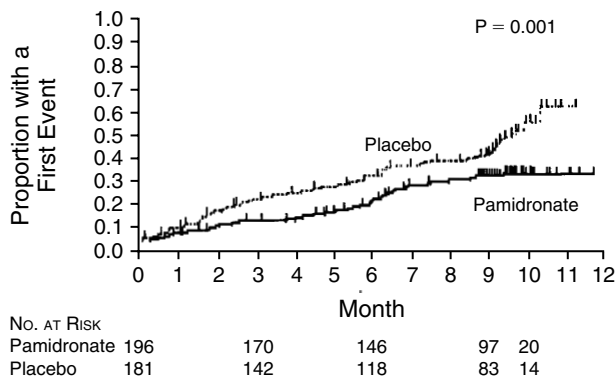Placebo   181   142   118   83   14

Figure 1. Kaplan–Meier Estimates of the Time to the First Skeletal Event in the Study Patients.

Table 3. Occurrence of Skeletal Events by the End of Nine Cycles of Treatment, According to Stratum.

Type of Event	Stratum 1			Stratum 2		
	Pamidro-nate (N = 133)	Placebo (N = 114)	P value	Pamidro-nate (N = 63)	Placebo (N = 67)	P value
	no. of patients (%)			*no. of patients (%)*		
Any*	29 (22)	38 (33)	0.04	18 (29)	36 (54)	0.004
Pathologic fracture	19 (14)	31 (27)	0.01	15 (24)	23 (34)	0.19
Radiation treatment to bone	17 (13)	17 (15)	0.63	11 (18)	23 (34)	0.03

*Except hypercalcemia.

cebo group had no change in the response of osteolytic lesions. There were no differences in the changes in the response of osteolytic lesions in the remaining patients.

Quality of Life

At the final evaluation, which occurred before the nine-month visit or at that time, the patients in the pamidronate group had significant decreases from base line in scores for bone pain (Fig. 2), no increase in scores for analgesic-drug use, and no deterioration in ECOG performance status or scores for quality of life (data not shown). In contrast, the patients in the placebo group had increased scores for bone pain, increased scores for analgesic-drug use, and worsening of both ECOG performance status and quality of life on the Spitzer index. The changes in scores for performance status and analgesic-drug use from base line to the final evaluation differed significantly between the two groups.

Metabolic Markers of Tumor and Bone

There were no differences between treatment groups with respect to changes in serum concentrations of myeloma protein and beta$_2$-microglobulin or in Bence Jones proteinuria. The serum and urinary markers of both bone resorption and bone formation were reduced in the pamidronate group throughout the treatment period, but they did not change in the placebo group. The median decreases from base line in two markers of bone resorption — the ratio of urinary calcium to urinary creatinine (with the concentration of each expressed in millimoles per liter) and the ratio of urinary hydroxyproline to urinary creatinine (with the concentration of each expressed in millimoles per liter) — were 32 percent and 26 percent, respectively, at the final measurement in the patients in the pamidronate group. In the pamidronate group, there were also decreases from base line of 56 percent in the serum bone alkaline phosphatase concentration and of 50 percent in the serum osteocalcin concentration (markers of bone formation) at the final measurement.

Adverse Events

The infusions of pamidronate were tolerated well. The incidence of adverse effects and toxic effects of chemotherapy was similar in the two groups. Two patients in the pamidronate group were withdrawn from the study because of drug-related toxic effects: an apparently allergic reaction and hypocalcemia (serum calcium, 7.5 mg per deciliter [1.9 mmol per liter]).

Outcome

Overall survival did not differ significantly between the two treatment groups on the basis of a median follow-up of 17 months. The estimated median survival was 28 months in the pamidronate group and 23 months in the placebo group (Fig. 3).

Discussion

Approximately 80 percent of patients with multiple myeloma have radiographic evidence of skeletal destruction, which frequently results in bone pain and pathologic fracture.[2] Even patients who respond to chemotherapy may have progression of skeletal disease,[8,20] and recalcification of osteolytic lesions is rare. Corticosteroids, sodium fluoride either alone or in combination with calcium, and androgenic steroids do not alter the progression of skeletal disease in myeloma.[20-23] Because they inhibit osteoclastic resorption of bone, bisphosphonates would be expected to be effective in treating this bone disease. However, the results of two large trials of oral etidronate[8] and clodronate[10] were unimpressive, perhaps because of poor bioavailability of the drug[24,25] or lack of potency. Pamidronate is a second-generation bisphosphonate that is 100 times more potent than etidronate and 10 times more potent than clodronate in preventing bone resorption in vivo.[11] In open-label studies, pamidronate reduced biochemical markers of bone resorption and bone pain in patients with myeloma.[13,14,26]

We found that treatment with pamidronate resulted in substantial clinical benefits with regard to the bony complications of stage III multiple myeloma in patients receiving either first-line chemotherapy or subsequent
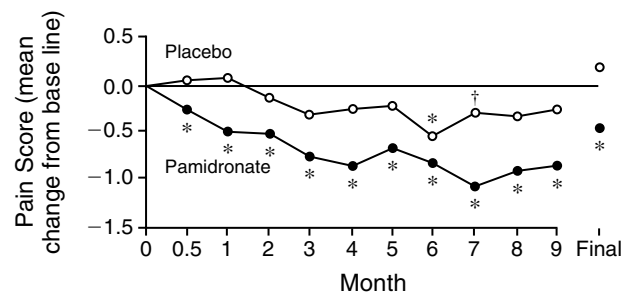

Figure 2. Mean Changes in the Pain Score for Patients Who Had Pain at Base Line.

"Final" refers to the last score obtained for each patient. At all data points marked with a symbol, the differences were statistically significant at P = 0.05 or less; the asterisks denote comparisons with the base-line value in the same treatment group, and the dagger denotes the comparison between treatments at the time shown.
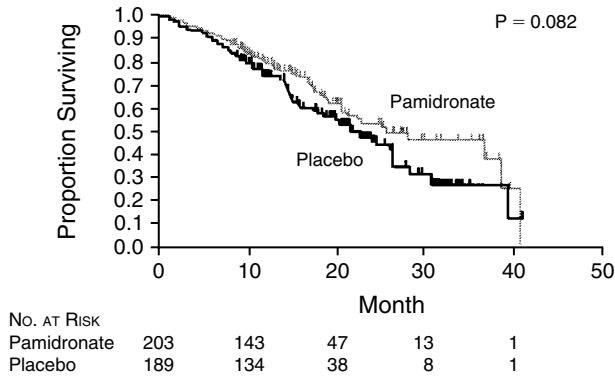
Figure 3. Kaplan–Meier Estimates of Survival in the Study Patients.

Survival was measured from the time of randomization to March 1, 1994. In the pamidronate group, there were 67 deaths and a median survival of 28 months; in the placebo group, there were 77 deaths and a median survival of 23 months. The median duration of follow-up was 17 months.

regimens. Morbidity was reduced at every evaluation during pamidronate treatment. Both the need for radiation treatment to bone and episodes of hypercalcemia were reduced after three cycles of treatment, and there was a significant reduction in pathologic fractures by the end of nine cycles. Furthermore, a longer time passed before there was any skeletal event, pathologic fracture, or need for radiation treatment to bone in the patients treated with pamidronate.

To analyze the efficacy of the study drug with respect to the status of myeloma disease, we stratified the patients at entry into the study according to whether their current chemotherapy was a first-line treatment (stratum 1) or a second or subsequent treatment (stratum 2). First-line systemic chemotherapy may result in remission and often palliates bone pain associated with advanced multiple myeloma.[27,28] In general, rates of remission are lower and bone pain decreases less in patients who receive another type of therapy when their disease has progressed during or after an initial treatment regimen.[29,30] This pattern was illustrated in the present study by the fact that among the patients receiving placebo, the proportion who required radiation therapy to bone was larger in stratum 2 than in stratum 1 (34 percent vs. 15 percent, respectively). Most patients treated with radiation to bone were so treated to relieve bone pain. Pamidronate reduced the proportion of patients in stratum 2 who required radiation therapy to bone (P=0.03), suggesting that the drug palliates bone pain associated with bone disease in myeloma when chemotherapy no longer does so effectively.

Conversely, although the proportion of patients with pathologic fractures was smaller in the pamidronate group than in the placebo group, this difference was statistically significant only in stratum 1. This finding may be due to the smallness of the sample studied or to the fact that bone destruction was advanced in the pa-

tients in stratum 2. In addition, the treatment groups did not differ with respect to the healing of osteolytic lesions as detected on plain x-ray films, but there were more pathologic fractures in the placebo group. Either plain x-ray films may not be a sensitive means of assessing such healing or pamidronate may have increased the mechanical strength of the remaining bone that had not yet been destroyed by osteolysis.[31,32]

Biochemical markers of bone resorption and bone formation both decreased in the pamidronate-treated patients. The decrease in bone resorption is thought to be mediated by the inhibitory effect of pamidronate on osteoclastic function. The decrease in markers of bone formation may have been due to the inhibition of bone resorption. Normally, the resorption of old bone by osteoclasts is coupled to the formation of new bone by osteoblasts. Thus, a decrease in bone resorption eventually results in a decrease in bone formation.[33] The finding that after nine cycles of treatment the proportion of patients with pathologic fractures was significantly smaller in the pamidronate group than in the placebo group suggests that the sustained decrease in markers of bone formation may have been a normal physiologic response without negative clinical consequences.

There was no difference in survival between the pamidronate-treated and the placebo-treated patients, and the profile of adverse events was similar in the two groups. The absence of a difference in survival may have been due to the heterogeneity of the chemotherapeutic regimens the patients were receiving, the short period of follow-up (median, 17 months), or the fact that pamidronate does not treat the underlying myeloma directly.

We conclude that monthly infusions of pamidronate are an effective adjunctive treatment for the palliation of the destructive skeletal events that are frequent in patients with multiple myeloma. Treatment with pamidronate is safe and well tolerated, and it improves patients' comfort and well-being.

APPENDIX

In addition to the study authors, the following principal investigators of the Myeloma Aredia Study Group participated in this study: R. Alexanian, Houston; J. Ansell, Worcester, Mass.; M. Baumann, Dayton, Ohio; G. Beltran, New Orleans; E. Besa, Philadelphia; R. Blanchard, Boston; D. Blayney, Glendora, Calif.; E. Braud, Springfield, Ill.; D. Bryson, Loma Linda, Calif.; R. Burningham, Portland, Oreg.; M. Campbell, Grand Rapids, Mich.; V. Canfield, Oklahoma City; J. Craig, Shreveport, La.; F. Cummings, Providence, R.I.; T. Dobbs, Knoxville, Tenn.; R. Dreicer, Iowa City, Iowa; W. Dugan, Indianapolis; P. Eisenberg, Greenbrae, Calif.; J. Feldmann, Mobile, Ala.; C. Freter, Washington, D.C.; I. Gill, Riverside, Calif.; D. Glover, Philadelphia; G. Gross, Tyler, Tex.; J. Harris, Fargo, N.D.; D. Hild, Hartford, Conn.; K. Hussein, Oklahoma City; J. Isaacs, Phoenix, Ariz.; A. Kaufman, Sellersville, Pa.; J. Kessler, Hampton, Va.; R. Levenson, Seattle; F.B. Lewis, St. Paul, Minn.; P. Mena, Burbank, Calif.; P. Michael, Las Vegas; A. Miller, Memphis, Tenn.; G. Monaghan, Columbia, Mo.; J. Moore, Tulsa, Okla.; J. Mortimer, St. Louis; L. Nathanson, Mineola, N.Y.; R. Navari, Birmingham, Ala.; K. Pandya, Rochester, N.Y.; T. Panella, Knoxville, Tenn.; G. Parker, Oklahoma City; M. Perry, Columbia, Mo.; M. Raab,

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